Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Addendum to NDA 205-677 Package

Date:	**November 4, 2013**
To:	**Members of the Peripheral and Central Nervous System Drugs Advisory Committee**
From:	**Division of Biometrics I** **Office of Biostatistics** **Office of Translational Science** **FDA, CDER**
Subject:	**Addendum to Statistical Review**
Product:	**Tasimelteon**

This memorandum is an addendum to the Statistical Review. It summarizes the important events for Study 3201 and provides updated and additional analysis of clinical endpoints for Study 3201.

1. Summary of Important Events for Study 3201

Table 1 presents the summary of important events that occurred in Study 3201. In the original protocol, the primary endpoint proposed by the sponsor was nTST and the proposed sample size was 160 patients, based on the postulated mean treatment difference of 39 minutes and standard deviation of 66 minutes. In Amendment 6 submitted to the Agency, the sample size was changed from 160 to 100 patients, based on the new postulated mean treatment difference of 30 minutes and standard deviation of 45 minutes. In Amendment 9, the primary endpoint was changed to entrainment and the sample size was reduced to 84 patients. At the time of Amendment 9 (May 21, 2012), 95% of the patients were randomized and 56% of the patients completed the study.

Amendment 11 was dated on December 11, 2012 and the trial data was unblinded on December 12, 2012. It is unclear to us how much these changes might have impacted the trial results.

Table 1: Summary of Important Events for Study 3201

Study 3201 Important Events	Date	Primary Endpoint	Sample Size	Note
Original	5/24/2010	nTST	160	postulated mean difference =39 mins and std=66 mins
First Patient Enrolled	8/25/2010			
Amendment 6	8/8/2011	nTST	100	postulated mean difference =30 mins and std=45 mins
Amendment 9	5/21/2012	Entrainment	84	80/84 patients (95%) randomized; 47/84 patients (56%) completed
Last Patient Completed	10/29/2012			
Amendment 11	12/11/2012	Entrainment	84	
Data Unblinding	12/12/2012	Entrainment	84	

Source: Reviewer's Analysis

2. Updated and additional Analysis of Clinical Endpoints for Study 3201

In Section 3.2.3.4 and Section 3.2.3.5 of the Statistical Review (dated Oct. 18, 2013), the results of ANCOVA analysis and permutation ANCOVA analysis were presented. In these two analyses, variable SITEGR1 was used as the pooled sites in the ANCOVA model and the 6 patients without SITEGR1 information was grouped as if they came from one site. However, at the Late Cycle Meeting with the sponsor on October 30, 2013, the sponsor informed the Agency that SITEGR1 was defined only for sponsor ITT population (n=78) and variable SITEGR3 was defined for all the 84 patients. The Statistical Analysis Plan suggests that the pooling strategy was prespecified. However, the Study Report shows that the randomization was not stratified by study site. Normally, if the randomization isn't stratified by study site, the site isn't necessarily included in the analysis model to comply with the trial design. Table 2 presents the p-values of the following four analyses (using the sponsor's pre-specified pooling strategy):

- ANCOVA analysis without including sites in the model
- Permutation ANCOVA analysis without including sites in the model
- ANCOVA analysis including sites in the model

- Permutation ANCOVA analysis including sites in the model

Table 2: Summary of ANCOVA and Permutation ANCOVA Analysis

Analysis	LQ-nTST	UQ-dTSD	MoST	CGIC	nTST	dTSD
ANCOVA without Sites	0.0510	0.0118	0.0366	0.0080	0.1149	0.0166
Permutation ANCOVA without Sites	0.0516	0.0111	0.0361	0.0083	0.1168	0.0154
ANCOVA with Sites	0.0232	0.0031	0.0229	0.0104	0.0658	0.0026
Permutation ANCOVA with Sites	0.0236	0.0032	0.0218	0.0138	0.0684	0.0024

Source: Reviewer's Analysis

Please note that the p-values in this able replace the p-values presented in Table 12 and Table 16 in the original Statistical Review (dated Oct. 18, 2013).

In this reviewer's view, permutation ANCOVA without sites in the analysis model is appropriate and the overall conclusion given in the original statistical review remains the same.